

have diverse activities in embryonic development and some have no role in development.”

Further, in the Examiner’s opinion, “the particular transforming growth factors of the Akhurst abstract had been well characterized for their activity [whereas] Applicant’s GDF-1 had not been.”

Applicants respectfully note that, according to the Akhurst abstract submitted, the reference was published in 1990, which is the year that the earliest priority application to the present application was filed. Therefore, the Akhurst reference is an appropriate measure of what was known in the art relating to transforming growth factors at the time the present invention was made. According to the Akhurst abstract, “each” of the TGF-beta family members identified at that time played a pivotal role in embryonic processes. There is no suggestion that other TGF-beta family members known at that time played a role that did not relate to development, and the Examiner has provided no evidence to suggest that TGF-beta members known at that time were thought to “have no role in development.”

Furthermore, it is Applicants’ understanding upon reading the new utility guidelines (FR, Vol. 66, No. 4, January 5, 2001) that it is perfectly acceptable to assert a specific, substantial and credible utility on the basis of “homology to existing nucleic acids or proteins having an accepted utility.” According to the FR Notice, a rigorous correlation is not necessary; only a “reasonable” correlation (see the FR Notice, page 1096, middle column continuing into right-hand column). As stated therein, “When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein” (with emphasis). Id.

According to the new utility guidelines, “the asserted utility must be accepted by the examiner unless the Office has sufficient or sound reasoning to rebut such an assertion” (with emphasis) Id. The Examiner rejects the asserted utility on the basis that the members of the

TGF-beta family exhibit diverse activities, and that some members have roles not related to embryonic development. However, the Examiner provides no evidence that those of skill in the art at the time the invention was made would have believed that members of the TGF-beta superfamily exhibit such diverse activities as to preclude prediction of function based on this family assignment. In contrast, according to the Akhurst abstract, there had been five type beta transforming growth factors (TGF betas) identified at the priority date of the invention, each of which was found to play "a pivotal role in embryonic processes."

Thus, at the time the invention was made in 1990, one of skill in the art would have reasonably predicted that a member assigned to the TGF-B superfamily would play a role in embryonic development, and in the growth and differentiation of tissues, given that the five members identified at that time were shown to play a pivotal role in embryonic development. Indeed, according to the instant specification at page 1, "a growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis [had] been found to be structurally homologous to transforming growth factor B." On that basis, and in view of the homology of GDF-1 to TGF-beta, the present inventor predicted that the GDF-1 protein was likely to play an important role in mediating developmental decisions related to cell differentiation (see page 2, lines 25-29). Moreover, it was perfectly reasonable on the basis of that prediction and the homology demonstrated according to the rules promulgated by the Office for Applicants to assert that the claimed protein would find utility in prenatal screens to detect developmental abnormalities, as disclosed on pages 12-13 of the specification.

The Examiner has provided no evidence to suggest that these predictions, which were based on the known activities of TGF-beta at the time, were unreasonable. She has presented no evidence to back up the assertion that TGF-beta activities were thought to be so diverse at that time so as to make these predictions unreasonable. Furthermore, the argument that one could not have predicted the role of the GDF-1 protein based on homology with this superfamily should be

re-evaluated in view of recent evidence with GDF-1  $-/-$  knock-out mice that demonstrates that, in fact, Applicant's predictions were correct.

For instance, as the present inventor and others have shown in a recently published paper (Rankin et al., 2000, Regulation of left-right growth patterning in mice of growth/differentiation factor-1, Nature Genetics 24: 262-66), GDF-1 plays a pivotal role in embryogenesis. A knockout mouse was generated in order to examine the biological function of GDF-1, which exhibited a spectrum of defects related to left-right axis formation in embryos, including misplacement of internal organs (Fig. 2), developmental defects in organs and cardiac abnormalities (Fig. 3). The authors concluded that these findings indicate that GDF-1 is essential for proper establishment of the left-right axis in mice, and is required for the expression of many genes expressed downstream from *gdf1* during development.

The Examiner dismisses the Rankin reference because it was published well after the filing date of the invention, and because knock-out mice were not routinely produced at the time of the invention. The Examiner is correct to point out that the Rankin paper was published several years after the priority date, as was she correct to note that the experiments reported in the Ebendal declaration were performed after the priority date of the invention. However, Applicants are not claiming knockout mice, nor are they claiming the methods reported in the Ebendal declaration. The Rankin reference and the Ebendal declaration were submitted to demonstrate that the GDF-1 protein has the utilities that were predicted in the specification, and are suitable as evidence for that purpose.

Thus, results with the GDF-1  $-/-$  knockout mouse prove that GDF-1 is required for the proper development and positioning of organs during embryogenesis. This is consistent with the function of GDF-1 predicted in the specification (page 2, lines 25-29), and the results in the specification showing the expression of GDF-1 during embryogenesis (see Example 4 and Fig. 6). These results also suggest that the asserted utility of GDF-1 in prenatal screens for abnormal

development is a reasonable utility for the disclosed protein, given that it has now been confirmed that aberrant expression of GDF-1 has significant and substantial effects on embryonic development. A reasonable utility for the GDF-1 protein translates to a reasonable utility for the DNA encoding that protein, as well as for vectors, host cells and methods of recombinant production.

Thus, at the time the application was filed, the TGF-beta super family was known to comprise proteins involved in embryonic development, a function that Applicants predicted that GDF-1 would share. Further, Applicants have now shown that GDF-1 does possess the predicted function, thereby supporting the disclosed utilities, i.e., use in prenatal screening for developmental defects. And as noted above, according to the new utility examination guidelines, it is perfectly acceptable to predict a specific, substantial and credible utility on the basis of homology to existing nucleic acids or proteins having an accepted utility.

The Examiner asserts that in contrast to the TGF-beta family members known at the priority date of the invention, Applicants' GDF-1 had not been well characterized with regard to activity. However, this statement seems to disregard the new utility guidelines set forth by the Office, which permit utility to be asserted on the basis of homology to existing nucleic acids or proteins having a well-established utility. As acknowledged in the Office Action, GDF-1 proteins are 26-52% similar to TGF-B family members on the amino acid level. Moreover, according to the specification at the paragraph bridging pages 19-20, GDF-1 contains all of the invariant amino acids present in the C-terminal 122 amino acids of other TGF-B superfamily members, including the seven characteristic cysteine residues as well as many of the other most highly conserved amino acids. For instance, like the other family members, the C-terminal portion of the predicted GDF-1 polypeptide is preceded by a pair of arginine residues at positions 236-37. Thus, GDF-1 contains sufficient homology to be assigned to the TGF-beta superfamily, as substantiated by the similar assignment of other GDF proteins identified subsequently to GDF-1.

Thus, given that the new utility examination guidelines explicitly state that it is permissible to assert a credible utility on the basis of homology to a family of proteins having a well-established utility, and given that the inventors predicted and have now proven that GDF-1 would share the utility that had been well-established for members of the TGF-beta super family at the time the application was filed, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U. S. C. §101 and the enablement provision of §112, first paragraph.

Claims 4-7, 22, 24, 25, 30, 34 and 35 were also rejected under the written description section of 35 U.S.C. § 112, first paragraph. According to the Office Action, the Examiner maintains her position that the specification fails to describe a family of GDF-1 proteins as broadly as claimed, and that no structural features have been defined as limitations of the claims. Applicants respectfully maintain their traversal.

Applicants respectfully note again that the specification discloses that the human and murine GDF-1 proteins are 87% identical in the region beginning with the first conserved cysteine and extending to the C-terminus (see page 31, lines 19-20). Thus, this specific domain of GDF-1 is quite highly conserved across species, and would constitute a structural feature for identifying a GDF-1 protein.

Furthermore, the instant specification does disclose an assay for identifying a GDF-1 gene, in that a probe generated from the full length murine open reading frame of GDF-1 hybridized specifically to the human gene in Southern hybridization (see Fig. 14 legend at page 9, and the relevant discussion at pages 31-32). As also shown in Figure 5, even at high stringency, a murine GDF-1 probe identified a single prominent band in both human and hamster genomic DNA. The genomic sequences identified by these hybridization experiments could be readily cloned and sequenced to obtain the corresponding protein sequence using techniques that were well known at the time the application was filed.

The Office Action inquires as to why the structure of genomic sequences should be considered to be described in the specification. Applicants respectfully submit that the pending claims are not directed to genomic DNA sequences, but rather to proteins. Nevertheless, Applicants respectfully submit that the present application was filed after the publication of the popular Sambrook Molecular Cloning manual (2<sup>nd</sup> edition), which standardized many of the cloning procedures now used to identify and isolate genomic DNAs. Indeed, given the existence of the Sambrook manual at the time the present invention was filed, those of skill in the art would have surely seen that the inventor was in possession of the genomic DNA for the GDF-1 protein upon reading the present disclosure, and that such genomic DNA could be easily used to identify the corresponding protein sequence.

Thus, having full knowledge of the techniques that were well-known in the art at the time the invention was made, one of skill in the art reading the present disclosure and seeing that the disclosed coding sequences could be used as a probe to specifically identify genomic sequences by hybridization would have immediately seen that the present inventor was in possession of both DNA sequences encoding a genus of GDF-1 proteins as well as the corresponding protein sequences themselves. Furthermore, given the extent of homology between human and mouse GDF-1 shown in the specification, and the fact that probes generated from these sequences cross-hybridize specifically to the GDF-1 gene in alternative species using hybridization conditions specifically defined in the disclosure, it would be clear to those skilled in the art upon reading the present disclosure that Applicants were in possession of the claimed invention at the time the application was filed. In view of these remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, written description, is respectfully requested.

As a final matter, the Examiner has noted that page 9 does not appear to provide support for claims 34-35. Applicants apologize for any inconvenience to the Examiner, and note that the requisite support may be found on page 10, lines 8-9, where it is disclosed that 20X SSC is

defined as 3M sodium chloride/0.3M sodium citrate. So, by extension, 2X SSC would be defined as stated in these claims. Page 9, lines 11-12, gives support for washing at 68°C in 2X SSC, and page 17, lines 9-13 provide support for hybridization at 65°C.

All issues raised by the Office Action dated March 12, 2002, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).


Again, if the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully urged to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,

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